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System-size resonance for intracellular and intercellular calcium signaling

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ABSTRACT

Dynamical behaviors of unidirectionally, linearly coupled as well as isolated calcium subsystems are investigated by taking into account the internal noise resulting from finite system size and thus small numbers of interacting molecules. For an isolated calcium system, the internal noise can induce stochastic oscillations for a steady state close to the Hopf-bifurcation point, and the regularity of those stochastic oscillations depends resonantly on the system size, exhibiting system-size resonance. For the coupled system consisting of two subsystems, the system-size resonance effect observed in the subsystem subject to coupling is significantly amplified due to the nontrivial effects of coupling.

1. Introduction

In recent years, the influence of internal fluctuations on intrinsic dynamics has been intensively studied in biochemical processes, such as in calcium signaling [1–3], genetic regulations [4], circadian rhythms [5], and neuron spikings [6,7]. The investigation of internal fluctuations in nonlinear systems has led to the emergence of novel concepts such as system-size resonance (SSR). So far, mainly two types of SSR have been reported. One is that the behavior of an array of coupled noisy dynamical elements is the most ordered when the number of elements is optimal [8–10]. The other is that internal noise originating from the random fluctuations in finite-size biochemical systems are used to extract coherent signals and there are the strongest periodicities at a certain system size [11–13]. For instance, ion channel clusters of optimal sizes can enhance the encoding of a subthreshold stimulus [11], and optimal intracellular calcium signaling appears at a certain size or distribution of the ion channel clusters [12,13]. Recently, there has been increasing interests in coupled oscillators. Especially interesting is the phenomenon of array-enhanced coherence resonance (AECR), where the coherence can be significantly improved when the noisy excitable elements are coupled [14–16]. The influence of internal noise has been taken into account in coupled oscillators in biosystems [17–19]. For example, conductance noise induces frequency and phase synchronization in populations of weakly coupled neurons [17]. Internal noise resulting from finite system size makes the doublets of calcium oscillators synchronized [18,19]. Intercellular calcium signals are propagated in multicellular hepatocyte systems as well as in the intact liver. Some interhepatocyte Ca^{2+} signals are unidirectional for a given agonist [20]. However, little work has been done forward the understanding of the influences of coupling on the SSR phenomenon.

As the second messenger, calcium ions play an important role in a variety of cell types. Their oscillations control the birth, life, death of cell, tune the living process of cell, and enhance the efficiency and specificity of gene expression [21]. Calcium ion is therefore an integral part of the information-processing machinery in living organisms, and its diverse functions have been studied intensively [22–24]. Moreover, SSR phenomena have been achieved in calcium systems [1,2]. Nevertheless, to the best of our knowledge, influences of coupling on the SSR behavior in calcium system have gained a little insight. While many models have been developed to explain calcium oscillations, most of these models focus on the simple periodic oscillations [25,26] and only a few models are able to display complex periodic oscillations.

In this research, the Kummer model [27] was adopted to gain more insight into the influence of internal noise. This model is capable of displaying both simple and complex dynamic behavior [27]. By constructing a mesoscopic stochastic model, calculations show that the internal noise originating from finite system size is able to extract an inherent periodic signal of the system in a resonant manner at the point close to the supercritical Hopf bifurcation, indicating the occurrence of SSR. Additionally, the

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phenomenon of the SSR also appears in the periodic bursting regime due to the influence of internal noise. Later, two such calcium systems are coupled unidirectionally to explore how the SSR behavior changes with the variation of the coupling strength. It was found that SSR behavior still exists in each subsystem in the presence of coupling, and the SSR effect of the subsystem is significantly enhanced by increasing the coupling strength. This is an essential difference from the work done by Xin et al. [28], where the subsystems are bidirectionally coupled.

2. Model description

The model used here is able to display simple and complex behavior of calcium, depending on the kinetics of the receptor complex i.e., the agonist-specific receptor [29]. After the binding of an agonist to the extracellular side of a membrane-bound receptor molecule, the G_α subunit at the intracellular side of the receptor-coupled G-protein is activated. The activated G-protein in turn stimulates a phospholipase C (PLC), which leads to the production of IP_3, which diffuses through the cell and binds to receptors at the endoplasmic reticulum (ER). This leads to the liberation of calcium ion from endoplasmic reticulum and in some cases to the inflow of calcium ion from extracellular space [27]. The model of a single cell can be described by the following equations:

$$\begin{aligned}
\frac{dw}{dt} &= k_1 + k_2 w - \frac{k_3 w x}{w + K_4} - \frac{k_5 w x}{w + K_6},\\
\frac{dx}{dt} &= k_7 w - \frac{k_8 x}{x + K_9},\\
\frac{dy}{dt} &= \frac{k_{10} x y z}{z + K_{11}} + k_{12} x + k_{13} w - \frac{k_{14} y}{y + K_{15}} - \frac{k_{16} y}{y + K_{17}},\\
\frac{dz}{dt} &= -\frac{k_{10} x y z}{z + K_{11}} + \frac{k_{16} y}{y + K_{17}},
\end{aligned} \tag{1}$$

where w denotes the concentration of active G_α subunits of the G-protein, which are responsible for the activation of PLC. $\underline{x}$ refers to the concentration of active PLC. $\underline{y}$ is the concentration of free calcium ions in the cytosol, and $\underline{z}$ denotes the concentration of calcium in the ER. More details of the model can be found in Ref. [27]. Parameter values used in this study are: $k_1=0.09$, $k_3=0.64$, $k_4=0.19$, $k_5=4.88$, $k_6=1.18$, $k_7=2.08$, $k_8=32.24$, $k_9=29.09$, $k_{10}=5.0$, $k_{11}=2.67$, $k_{12}=0.7$, $k_{13}=13.58$, $k_{14}=153.0$, $k_{15}=0.16$, $k_{16}=4.85$, and $k_{17}=0.05$. $\underline{k_2}$ is the concentration of the agonist and is selected as the control parameter.

Deterministic equations could correctly describe the dynamics of the processes that involve macroscopically large quantities. When using the deterministic equations, one computes continuous concentrations of the participating species. However, biochemical reactions in the cell involve only a small number of molecules due to small cell volume. Interactions of a small number of molecules demand a stochastic approach, because internal fluctuations cannot be neglected anymore [30]. Biochemical reactions in the cell are governed by a chemical master equation, which is the basis for chemical simulation, but difficult to be solved analytically. The exact stochastic simulation algorithm introduced by Gillespie [31] has been widely used, which stochastically determines what the next reaction step is and when it will happen according to the transition probability of each reaction step. It has to be addressed that this model is a simplified one and does not include all the processes that are know to occur in the calcium system. However, the basic dynamical characteristics are caught in this model. Furthermore, in Kummer's following work, he has used the exact stochastic simulation (ESS) method to perform stochastic simulation with the core model [29]. In accordance with ESS method, the number of active G_α units is introduced as $\underline{W}$, the number of active PLC as $\underline{X}$, the number of calcium ions in the cytosol as $\underline{Y}$, and the number of calcium ions in the ER as $\underline{Z}$. As is described in Ref. [27], the model was constructed on the basis of previous experimental observations and data like those shown in Figs. 1 and 2 in Ref. [27], where the quantity is between 0 and 1000, and the unit of the calcium concentration is nM. In the present work, the results of calcium concentration by deterministic simulations are between 0 and 10. Therefore, the unit μM for concentration and μm^3 for the volume are chosen to give qualitative discussion. The concentration of the reactants are $w=\frac{\frac{W}{L}\times 10^6}{V\times 10^{-15}}=\frac{W}{VL}\times 10^{21}(\mu M)$, $x=\frac{X}{VL}\times 10^{21}(\mu M)$, $y=\frac{Y}{VL}\times 10^{21}(\mu M)$ and $z=\frac{Z}{VL}\times 10^{21}(\mu M)$, where L is the Avogadro's number. The volume $\underline{V}$ is used to convert concentrations into numbers of molecules and then regulate the intensity of internal noise. According to the model biochemical reactions in the cell can be grouped into eleven processes for the current model, and the corresponding transition probabilities for the processes are listed in Table 1. $a_1 \ldots a_{11}$ are transition rates, as are described in Table 1, where several reaction progresses have been eliminated according to the deterministic model.

The exact stochastic simulation algorithm can account for the internal noise exactly, but it is too time consuming when the system size is large. The chemical Langevin (CL) method [32] has proven to be an efficient simulation algorithm [33–35] to take internal noise into account if a macro-infinitesimal time scale exists in the system. CL equations for the current model are described as

$$\begin{aligned}
\frac{dW}{dt} &= (a_1 + a_2 - a_3 - a_4) + (\sqrt{a_1}\xi_1 + \sqrt{a_2}\xi_2 - \sqrt{a_3}\xi_3 - \sqrt{a_4}\xi_4),\\
\frac{dX}{dt} &= (a_5 - a_6) + (\sqrt{a_5}\xi_5 - \sqrt{a_6}\xi_6),\\
\frac{dY}{dt} &= (a_7 + a_8 + a_9 - a_{10} - a_{11})\\
&\quad + (\sqrt{a_7}\xi_7 + \sqrt{a_8}\xi_8 + \sqrt{a_9}\xi_9 - \sqrt{a_{10}}\xi_{10} - \sqrt{a_{11}}\xi_{11}),\\
\frac{dZ}{dt} &= (a_{11} - a_7) + (\sqrt{a_{11}}\xi_{11} - \sqrt{a_7}\xi_7).
\end{aligned} \tag{2}$$

Where $\xi_{i=1,\ldots,11}(t)$ are Gaussian white noises with $\langle \xi_i(t)\rangle = 0$ and $\langle \xi_i(t)\xi_j(t')\rangle = \delta_{ij}\delta(t-t')$. $a_1 \ldots a_{11}$ are transition rates, as are described in Table 1, where several reaction progresses have been eliminated according to the deterministic model. According to the relationship

Table 1
Stochastic transition processes and corresponding rates

Transition processes	Description	Transition rates
(1)$W\to W+1$	The spontaneous activation of G_α units	$a_1=V\cdot k_1$
(2)$W\to W+1$	The accelerated formation of active G_α after binding of agonist to the membrane receptor	$a_2=V\cdot k_2 w$
(3)$W\to W-1$	The inactivation of G_α units accelerated by active PLC	$a_3 = V\cdot\frac{k_3 w x}{w+K_4}$
(4)$W\to W-1$	Negative feedback of calcium-dependent kinase on G_α units	$a_4 = V\cdot\frac{k_5 w x}{w+K_6}$
(5)$X\to X+1$	The activation of PLC depends on the concentration of active G_α units	$a_5=V\cdot k_7 w$
(6)$X\to X-1$	The enzymatic inactivation of PLC	$a_6 = V\cdot\frac{k_8 x}{x+K_9}$
(7)$Y\to Y+1$ $Z\to Z-1$	The inflow of calcium from the internal stores	$a_7 = V\cdot\frac{k_{10} x y z}{z+K_{11}}$
(8)$Y\to Y+1$	The influx of calcium from the extracellular Space stimulated by IP_3	$a_8=V\cdot k_{12} x$
(9)$Y\to Y+1$	The influx of receptor-operated calcium	$a_9=V\cdot k_{13} w$
(10)$Y\to Y-1$	The pump of cytosol Ca^{2+} into the ER by ATP-dependent pumps	$a_{10} = V\cdot\frac{k_{14} y}{y+K_{15}}$
(6)$Y\to Y-1$ $Z\to Z+1$	The pump of cytosol Ca^{2+} into the extracellular space by ATP-dependent pumps	$a_{11} = V\cdot\frac{k_{16} y}{y+K_{17}}$